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July 6, 2009

Re: 6495-121945

To Whom It May Concern:

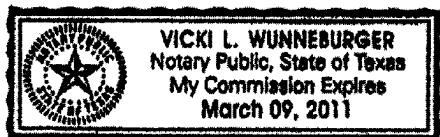
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We certify that the English translation conforms essentially to the original German language.

A handwritten signature in black ink that reads "Kim Vitray".

Kim Vitray
Operations Manager

Subscribed and sworn to before me this 6th day of July, 2009.



A handwritten signature in black ink that reads "Vicki L. Wunneburger".

Vicki Wunneburger
Notary Public

European Patent Application No. 0, 149, 200 A1
[Selected portions, as requested]

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**NEW 2-PHENYLMIDAZOLES, THEIR PRODUCTION, AND PHARMACEUTICALS
CONTAINING THESE COMPOUNDS**

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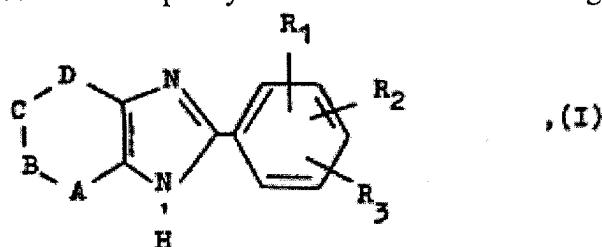
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[Abstract]

The invention concerns new 2-phenylimidazoles of the following general formula:



in which

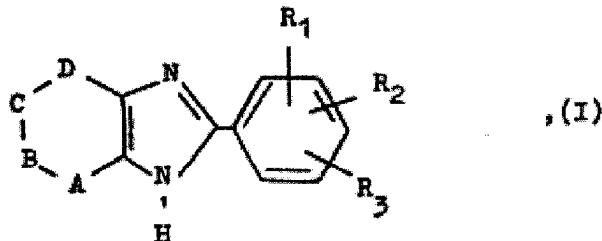
A to D and R₁ to R₃ have the meanings indicated in Claim 1, [it also concerns] their tautomers and their acid addition salts, in particular, their physiologically compatible acid addition salts, which have valuable pharmacological characteristics, in particular, an effect on the contractility of the heart muscle.

The compounds of general formula I can be prepared according to methods common for analog compounds.

* * *

Claims

1. 2-Phenylimidazoles of the general formula:



in which A, B, C, and D each have a nitrogen atom possibly substituted with a hydrogen atom or an alkyl group with 1 to 3 carbon atoms, a carbon atom substituted with a hydrogen atom, a halogen atom, a hydroxyl group, a benzyloxy group or an alkoxy group with 1 to 3 carbon atoms, or a carbonyl group, wherein, however, at least one of the radicals A, B, C, or D must be a nitrogen atom, possibly substituted with a hydrogen atom or an alkyl group, and another of the radicals A, B, C, or D, a carbon atom, substituted with a halogen atom, a hydroxyl, benzyloxy, or alkoxy group, or a carbonyl group;

R₁ represents a nitrile, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonyl, or alkanoylamino group; or

if A, B, C, and D, together with the radical of the molecule, do not represent 8-phenyl xanthine, in which the phenyl ring is unsubstituted in the 2- and/or 6-positions, [it] also [represents] an aminosulfonyl, alkylaminosulfonyl, or dialkylaminoaminosulfonyl group; or

if A represents a nitrogen atom substituted by a hydrogen atom or by an alkyl group, also an alkylmercapto, alkylsulfinyl, or alkylsulfonyl group, with 1 to 3 carbon atoms in each alkyl part; or

if A represents a nitrogen atom, possibly substituted by a hydrogen atom or an alkyl group, and the phenyl ring is substituted in the 2-position by an alkoxy or dialkylamino group, also a halogen atom, an alkyl, nitro, carbonyl, amino, alkylamino, dialkylamino, or benzyloxy group, or an alkoxy group in the 5-position, or also if the radicals A, B, C, and D, together with the imidazole ring, do not represent a theophylline radical, also an alkoxy group in the 4-position, wherein the alkyl part can contain 1 to 3 carbon atoms; or

if A represents a nitrogen atom substituted with a hydrogen atom or by an alkyl group, and R₂ and R₃ do not represent a hydrogen atom, also a halogen atom, a nitro, benzyloxy, hydroxysulfonyl, or alkoxy group with 1 to 3 carbon atoms; or

if A and at least one of the radicals B and D represent a nitrogen atom, possibly substituted with a hydrogen atom or an alkyl group, also a halogen atom, an alkyl, hydroxyl, benzyloxy, alkoxy, alkylmercapto, alkylsulfinyl, alkylsulfonyl, hydroxysulfonyl, nitro, amino, alkylamino, or dialkylamino group, wherein the alkyl part can contain 1 to 3 carbon atoms; or

if B and C simultaneously represent a nitrogen atom, possibly substituted with a hydrogen atom or an alkyl group, also a halogen atom, an alkyl, hydroxyl, benzyloxy, alkoxy, alkylmercapto, alkylsulfinyl, alkylsulfonyl, hydroxysulfonyl, nitro, amino, alkylamino, or diakylamino group, wherein the alkyl part can contain 1 to 3 carbon atoms; or

if A represents a nitrogen atom and C a nitrogen atom substituted with an alkyl group, also a benzyloxy, alkylmercapto, alkylsulfinyl, or alkylsulfonyl group, or if the radicals A, B, C, and D, together with the imidazole ring, do not represent a xanthine radical, also an alkyl, hydroxyl, alkoxy, nitro, amino, alkylamino, or dialkylamino group, wherein the alkyl part can contain 1 to 3 carbon atoms; or

if A represents a nitrogen atom and B a carbon atom substituted with an alkoxy group, also a halogen atom, an alkyl, nitro, amino, alkylamino, dialkylamino, hydroxyl, alkoxy, benzyloxy, alkylmercapto, alkylsulfinyl, alkylsulfonyl, hydroxysulfonyl, or carboxyl group, wherein each alkyl part can contain 1 to 3 carbon atoms;

R_2 and R_3 , which can be the same or different, represent hydrogen atoms, halogen atoms, alkyl, hydroxyl, alkoxy, benzyloxy, alkylmercapto, alkylsulfinyl, alkylsulfonyl, nitro, amino, alkylamino, dialkylamino, alkanoylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, nitrile, carboxyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, or dialkylaminocarbonyl groups, wherein the alkyl part can contain 1 to 3 carbon atoms, signify their tautomers and their acid addition salts.

2. 2-Phenylimidazoles of general formula I, in accordance with Claim 1, in which A, B, C, and D must represent a nitrogen atom, possibly substituted with a hydrogen atom or a methyl group, a carbon atom substituted with a hydroxyl, methoxy, or benzyloxy group, or a carbonyl group, wherein, however, at least one of the radicals A, B, C, or D must represent a nitrogen atom, possibly substituted with a hydrogen atom or a methyl group, and another of the radicals A, B, C, or D, must represent a carbon atom, substituted with a chlorine atom, a hydroxyl, methoxy, or benzyloxy group, or a carbonyl group;

R_1 represents a nitrile, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methoxycarbonyl, or acetylamino group; or

if A, B, C, and D, together with the radical of the molecule, do not represent 8-phenylxanthine, in which the phenyl ring is unsubstituted in the 2- and/or 6-positions, also an aminosulfonyl, methylaminosulfonyl, or dimethylaminosulfonyl group; or

if A represents a nitrogen atom, substituted with a hydrogen atom or a methyl group, also a methylmercapto, methylsulfinyl, or methylsulfonyl group;

if A represents a nitrogen atom, possibly substituted with a hydrogen atom or a methyl group, and the phenyl ring is substituted in the 2-position with a methoxy, ethoxy, propoxy, or dimethylamino group, also a chlorine or bromine atom, a methyl, nitro, amino, methylamino,

dimethylamino, or benzyloxy group, or a methoxy group in the 5-position, if the radicals A, B, C, and D, together with the imidazole ring, do not represent a theophylline radical, also a methoxy group in the 4-position; or

if A represents a nitrogen, substituted with a hydrogen atom or a methyl group, and R₂ and R₃ do not represent a hydrogen atom, also a chlorine or bromine atom, a nitro, hydroxysulfonyl, methoxy, ethoxy, propoxy, or benzyloxy group; or

if A and at least one of the radicals B or D represent a nitrogen atom, possibly substituted with a hydrogen atom or a methyl group, also a chlorine atom, a methyl, hydroxyl, benzyloxy, methoxy, ethoxy, propoxy, methylmercapto, methylsulfinyl, methylsulfonyl, hydroxysulfonyl, amino, methylamino, or dimethylamino group; or

if B and C simultaneously represent a nitrogen atom, possibly substituted with a hydrogen atom or a methyl group, also a chlorine atom, a methyl, hydroxyl, methoxy, ethoxy, propoxy, benzyloxy, methylmercapto, methylsulfinyl, methylsulfonyl, hydroxysulfonyl, nitro, amino, methylamino, or dimethylamino group; or

if A represents a nitrogen atom and C, a nitrogen atom substituted with a methyl group, also a methylmercapto, methylsulfinyl, or methylsulfonyl group, or if the radicals A, B, C, and D, together with the imidazole ring do not represent a xanthine radical, also a methyl, hydroxyl, methoxy, ethoxy, propoxy, nitro, amino, methylamino, or dimethylamino group; or

if A represents a nitrogen atom and B, a carbon atom substituted with a methoxy group, also a chlorine or bromine atom, a methyl, nitro, amino, methylamino, dimethylamino, hydroxyl, methoxy, ethoxy, propoxy, benzyloxy, methylmercapto, methylsulfinyl, methylsulfonyl, hydroxysulfonyl, or carboxyl group;

R₂ represents a hydrogen, chlorine or bromine atom, a methyl, hydroxyl, methoxy, ethoxy, benzyloxy, methylmercapto, methylsulfinyl, methylsulfonyl, nitro, amino, methylamino, dimethylamino, acetylamino, aminosulfonyl, methylaminosulfonyl, dimethylaminosulfonyl, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, or dimethylaminocarbonyl group; and

R₃ represents a hydrogen atom, a dimethylamino, hydroxyl, methoxy, ethoxy, or propoxy group, their tautomers, and their acid additional salts.

3. 2-Phenylimidazoles of general formula I, in accordance with Claim 1, in which A, B, C, D, and R₁ are defined in Claim 2, wherein R₁ is in the 4- or 5-position; R₃, in the 2-position, with the exception of the hydrogen atom, has the meanings mentioned for R₃ in Claim 2; and

R₂ represents a hydrogen, chlorine or bromine atom, a nitro, aminosulfonyl, or methylaminosulfonyl group, their tautomers, and their acid addition salts.

4. 2-Phenylimidazoles of general formula I, in accordance with Claim 1, in which A, B, C, D, R₁ and R₃ are defined as in Claim 2, and

R_2 represents a hydrogen atom, their tautomers, and their acid addition salts.

5. 2-Phenylimidazoles of general formula I, in accordance with Claim 1, in which A, B, C, and D are defined as in Claim 2; R_1 , in the 4-position, a benzoyl, methylmercapto, methylsulfinyl, methylsulfonyl, aminosulfonyl, methylaminosulfonyl, or dimethylaminosulfonyl group; R_3 , in the 2-position, represents a methoxy group; and R_2 , a hydrogen atom, and their tautomers, and their acid addition salts, in particular, their physiologically compatible acid addition salts with inorganic or organic acids.

6. 2-(2-Methoxy-4-methylsulfonylphenyl)-5H-imidazo[4,5-d]-pyridazin-4-one, its tautomers, and its acid addition salts.

7. Physiologically compatible acid addition salts with inorganic or organic acids, in accordance with Claims 1 to 6.

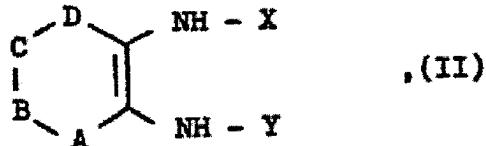
8. Medicines, containing a compound in accordance with Claims 1 to 6, or a physiologically compatible acid addition salt in accordance with Claim 7, in addition to one or more inert carrier substances and/or diluents.

9. Use of a compound, in accordance with Claims 1 to 6, or a physiologically compatible acid addition salt, in accordance with Claim 7, for the treatment of cardiac insufficiencies.

10. Method for the production of a medicine, characterized in that in a nonchemical way, a compound in accordance with Claims 1-6, or a physiologically compatible acid additional salt in accordance with Claim 7, is incorporated into one or more inert carrier substances and/or diluents.

11. Method for the production of new 2-phenylimidazoles in accordance with Claims 1-7, characterized in that

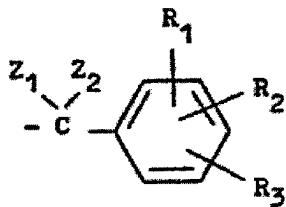
a) a compound of the following general formula:



possibly produced in the reaction mixture is cyclized, in which

A to D are defined as in Claim 1,

one of the radicals X or Y represents a hydrogen atom and the other of the two radicals X and Y or both radicals X and Y, a group of the following formula:



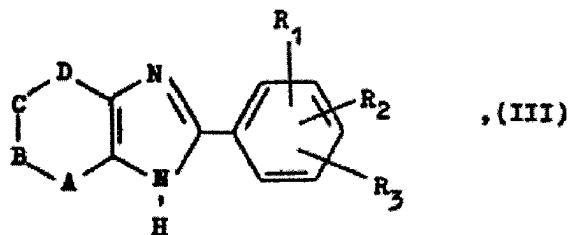
in which

R₁ to R₃ are defined as in Claim 1,

Z₁ and Z₂ can be the same or different, and represent a possibly substituted amino group, or hydroxyl or mercapto groups, possibly substituted with lower alkyl groups; or

Z₁ and Z₂, together represent an oxygen or sulfur atom, an imino group, possibly substituted with an alkyl group with 1 to 3 carbon atoms, an alkylenedioxy or alkylenedithio group with 2 or 3 carbon atoms; or

b) for the production compounds of general formula I, in which at least one of the radicals R₁, R₂, or R₃ represents an alkylsulfinyl or alkylsulfonyl group, a compound of the following general formula:

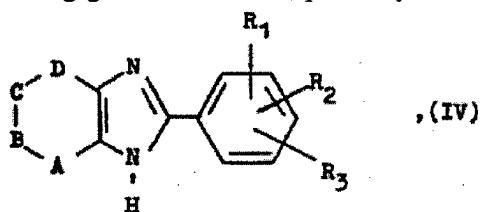


is oxidized

in which

A to D and R₁ to R₃ are defined as in Claim 1, wherein, however, at least one of the radicals R₁, R₂, or R₃ must represent an alkylmercapto or alkylsulfinyl group with 1 to 3 carbon atoms in each alkyl part, or

c) for the production of compounds of general formula I, in which at least one of radicals R₁, R₂, or R₃ represents a hydroxysulfonyl, aminosulfonyl, alkylaminosulfonyl, or dialkylaminosulfonyl group, a compound of the following general formula, possibly formed in the reaction mixture:



in which

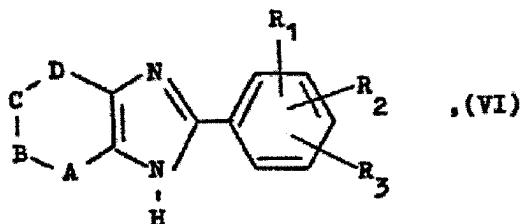
A to D and R₁ to R₃ are defined as in Claim 1, wherein, however, at least one of the radicals R₁, R₂, or R³ must represent a group of the formula USO₂, in which U represents a nucleophilic exit group, such as a halogen atom, is reacted with a compound of the following general formula:



in which

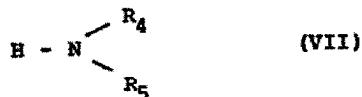
V represents a hydroxyl group or an amino group, possibly substituted with one or two alkyl groups with 1 to 3 carbon atoms; or

d) for the production of compounds of general formula I, in which at least one of the radicals R₁, R₂, or R₃ represents a carbonyl group substituted with an amino, alkylamino, or dialkylamino group, a compound of the following general formula:



in which

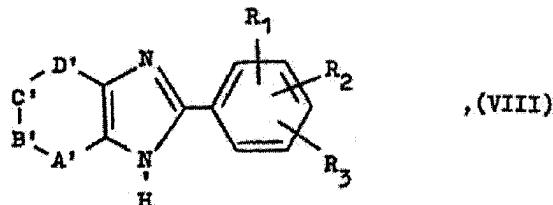
A to D and R₁ to R₃ are defined as in Claim 1, wherein, however, at least one of the radicals R₁, R₂, or R₃ represents the W-CO group, in which W must represent a hydroxyl group or a nucleophilic exit group, or a reactive derivative therefrom, is reacted with an amine with the following general formula:



in which

R₄ and R₅, which can be the same or different, represent hydrogen atoms or alkyl groups with 1 to 3 carbon atoms, or is reacted with a reactive derivative therefrom, if W represents the hydroxyl group; or

e) for the production of compounds with general formula I, in which at least one of the radicals A, B, C, or D represents a carbon atom or the carbonyl group, substituted with a hydroxyl, alkoxy, or phenylalkoxy group, a compound with the following general formula:



in which

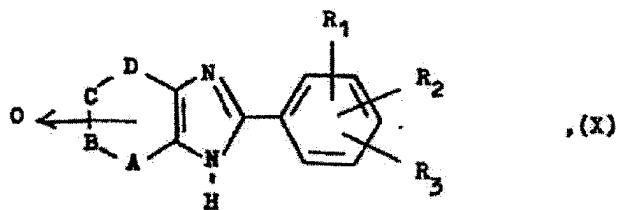
one of the radicals A', B', C', or D' represents a carbon atom, substituted with a halogen atom, and the other radicals A' to D' have the meanings mentioned for A to D in Claim 1, is reacted with a compound of the following general formula:



in which

R_6 represents a hydroxyl, alkoxy, or phenylalkoxy group, wherein the alkyl part can contain 1 to 3 carbon atoms; or

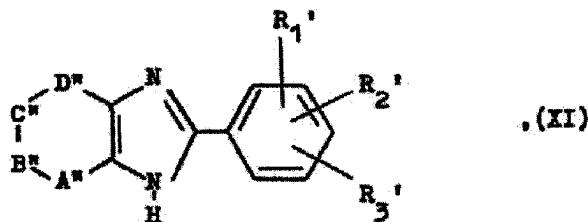
f) for the production of compounds of general formula I, in which at least one of the radicals A, B, C, or D represents a carbon atom, substituted by a hydroxyl group, or the carbonyl group, an N-oxide with the following general formula:



in which

A to D and R_1 to R_3 are defined as in Claim 1, is rearranged and possibly, subsequently, hydrolyzed; or

g) for the production of compounds of general formula I, in which at least one of the radicals A, B, C, or D represent a carbon atom, substituted with a hydroxyl group, or the carbonyl group and/or at least one of the radicals R_1 , R_2 , or R_3 represent a hydroxyl group, a compound of the following general formula:

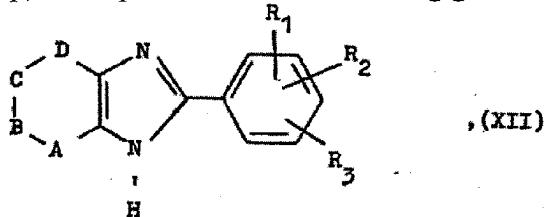


is debenzylized

in which

one of the radicals A'', B'', C'', or D'' represents a carbon atom, substituted with a benzyloxy group, and the other radicals A'' to D'' have the meanings mentioned for A to D in Claim 1, and/or at least one of the radicals R_1' , R_2' , or R_3' , a benzyloxy group and the other radicals R_1' to R_3' have the meanings mentioned for R_1 to R_3 in Claim 1; or

h) for the production of compounds of general formula I, in which at least one of radicals R₁ to R₃ represents an amino group, a compound with the following general formula:

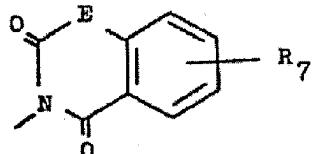


is reacted with hydrazine

in which

A to D are defined as in Claim 1,

at least one of the radicals R₁, R₂, or R₃ represents a group of the following formula:



wherein E is a bond or a methylene group, possibly substituted with alkyl groups with 1 to 3 carbon atoms; and

R₇ represents a hydrogen atom or a nitro group; and

the others of the radicals R₁ to R₃ have the meanings for R₁ to R₃ in Claim 1;

and if desired, a compound of general formula I, thus obtained, in which at least one of the radicals A, B, C, or D represents an alkoxyimine group and/or at least one of the radicals R₁, R₂, or R₃ represents a cyan group, is converted by means of hydrolysis and/or alcoholysis into a corresponding compound of general formula I, in which at least one of the radicals A, B, C, or D represents a carbonyl or hydroxymethine group and/or at least one of the radicals R₁, R₂, or R₃, an aminocarbonyl or alkoxy carbonyl group; and/or

a compound of general formula I, thus obtained, in which at least one of the radicals R₁, R₂, or R₃ represents a nitro group, is converted by means of reduction into a corresponding compound of general formula I, in which at least one of the radicals R₁, R₂, or R₃ represents an amino group; and/or

a compound of general formula I, thus obtained, in which at least one of the radicals R₁, R₂, or R₃ represents an amino group, is converted by means of alkanoylation into a corresponding compound of general formula I, in which at least one of the radicals R₁, R₂, or R₃ represents an alkanoylamino group; and/or

a compound of general formula I, thus obtained, in which at least one of the radicals R₁, R₂, or R₃ represents an amino group, is converted via its diazonium salt into a corresponding compound

of general formula I, in which one of the radicals R₁, R₂, or R₃ represents a halogen atom, a hydroxyl or cyan group; and/or

a compound of general formula I, thus obtained, in which one of the radicals R₁, R₂, or R₃ represents an aminocarbonyl group, is converted by means of dehydration into a corresponding compound of general formula I, in which R₁ represents a cyan group; and/or

a compound of general formula I, thus obtained, is converted into its acid addition salt, in particular, into its physiologically compatible acid addition salt, with an inorganic or organic acid.